



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁶ : A61K 31/44, C07D 401/04	A1	(11) International Publication Number: WO 98/07425 (43) International Publication Date: 26 February 1998 (26.02.98)
(21) International Application Number: PCT/US97/14731 (22) International Filing Date: 21 August 1997 (21.08.97) (30) Priority Data: 60/024,753 21 August 1996 (21.08.96) US Not furnished 19 June 1997 (19.06.97) US (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ADAMS, Jerry, L. [US/US]; 611 Forest Road, Wayne, PA 19087 (US). BOEHM, Jeffrey, C. [US/US]; 248 Anthony Road, King of Prussia, PA 19406 (US). (74) Agents: DINNER, Dara, L. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).	(81) Designated States: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW); Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM); European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE); OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: IMIDAZOLE COMPOUNDS, COMPOSITIONS AND USE (57) Abstract Novel 4,5 substituted imidazole compounds, and compositions for use in therapy as anti-inflammatory agents, and inhibitors cytokine p38/MAP kinase mediated diseases.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BV	Botswana	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	PL	Poland	PT	Portugal		
CN	China	KR	Republic of Korea	RO	Romania		
CU	Cuba	KZ	Kazakhstan	RU	Russian Federation		
CZ	Czech Republic	LC	Saint Lucia	SD	Sudan		
DE	Germany	LI	Liechtenstein	SE	Sweden		
DK	Denmark	LK	Sri Lanka	SG	Singapore		
EE	Estonia	LR	Liberia				

IMIDAZOLE COMPOUNDS, COMPOSITIONS AND USE

5

FIELD OF THE INVENTION

This invention relates to a novel group of imidazole containing compounds, processes for the preparation thereof, the use thereof in treating cytokine mediated diseases and pharmaceutical compositions for use in such therapy.

BACKGROUND OF THE INVENTION

Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are biological substances produced by a variety of cells, such as monocytes or macrophages. IL-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic β cells.

Dinarello, J. Clinical Immunology, 5 (5), 287-297 (1985), reviews the biological activities which have been attributed to IL-1. It should be noted that some of these effects have been described by others as indirect effects of IL-1.

Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis,

rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T Cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Monokines, specifically TNF, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with monokine activity such as by inhibition of monokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T-cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg *et al.*, The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, *et al.*, Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T-cells.

TNF has also been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, and the herpes virus for similar reasons as those noted.

Interleukin-8 (IL-8) is a chemotactic factor first identified and characterized in 1987. IL-8 is produced by several cell types including mononuclear cells, fibroblasts, endothelial cells, and keratinocytes. Its production from endothelial cells is induced by IL-1, TNF, or lipopolysaccharide (LPS). Human IL-8 has been shown to act on Mouse, Guinea Pig, Rat, and Rabbit Neutrophils. Many different names have been applied to IL-8, such as neutrophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil chemotactic factor (MDNCF), neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor.

IL-8 stimulates a number of functions in vitro. It has been shown to have chemoattractant properties for neutrophils, T-lymphocytes, and basophils. In addition it induces histamine release from basophils from both normal and atopic individuals as well as lysosomal enzyme release and respiratory burst from neutrophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without de novo protein synthesis, this may contribute to increased adhesion of the neutrophils to vascular endothelial cells. Many diseases are characterized by massive neutrophil infiltration. Conditions associated with an increased in IL-8 production (which is responsible for chemotaxis of neutrophil into the inflammatory site) would benefit by compounds which are suppressive of IL-8 production.

IL-1 and TNF affect a wide variety of cells and tissues and these cytokines as well as other leukocyte derived cytokines are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

There remains a need for treatment, in this field, for compounds which are cytokine suppressive anti-inflammatory drugs, i.e. compounds which are capable of inhibiting cytokines, such as IL-1, IL-6, IL-8 and TNF.

SUMMARY OF THE INVENTION

This invention relates to the novel compounds of Formula (I) and pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable diluent or carrier.

This invention also relates to a method of inhibiting cytokines and the treatment of a cytokine mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I).

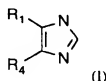
- 5 In particular the present invention relates to a method of treating a CSBP/RK/p38 kinase mediated disease, in a mammal in need thereof.

This invention more specifically relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

- 10 This invention more specifically relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

- This invention more specifically relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering
15 to said mammal an effective amount of a compound of Formula (I).

Accordingly, the present invention provides for a compound of the structure :



- 20 wherein:

R₁ is 4-pyridyl, pyrimidinyl, 4-pyridazinyl, 1,2,4-triazin-5-yl, quinolyl, isoquinolyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl, which heteroaryl ring is optionally substituted independently one to three times with Y, NHR_a, optionally substituted C₁₋₄ alkyl, halogen, hydroxyl, optionally substituted C₁₋₄ alkoxy, optionally substituted C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amino, mono and di- C₁₋₆ alkyl substituted amino, N(R₁₀)C(O)R_b, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur;

Y is X₁-R_a;

- 30 X₁ is oxygen or sulfur;

R₄ is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, C(Z)NR₇R₁₇, C(Z)OR₁₆, (CR₁₀R₂₀)_vCOR₁₂, SR₅, SOR₅, OR₁₂, halo-

- substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, ZC(Z)R₁₂, NR₁₀C(Z)R₁₆, or (CR₁₀R₂₀)_vNR₁₀R₂₀ and which, for other positions of substitution, is halogen, cyano, C(Z)NR₁₃R₁₄, C(Z)OR₃, (CR₁₀R₂₀)_m"COR₃, S(O)_mR₃, OR₃, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, (CR₁₀R₂₀)_m"NR₁₀C(Z)R₃, NR₁₀S(O)_mR₈.
- 5 NR₁₀S(O)_mNR₇R₁₇, ZC(Z)R₃ or (CR₁₀R₂₀)_m"NR₁₃R₁₄;
 v is 0, or an integer having a value of 1 or 2;
 m is 0, or the integer 1 or 2;
 m' is an integer having a value of 1 or 2,
 m" is 0, or an integer having a value of 1 to 5;
- 10 n is an integer having a value of 1 to 10;
 n' is 0, or an integer having a value of 1 to 10;
 Z is oxygen or sulfur;
 R₄ is C₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclylC₁₋₆ alkyl, heteroaryl, heteroarylC₁₋₆alkyl, wherein each of these moieties may be optionally substituted;
- 15 R₆ is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclyl, or heterocyclylC₁₋₄ alkyl;
 R₃ is heterocyclyl, heterocyclylC₁₋₁₀ alkyl or R₈;
 R₅ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₇R₁₇, excluding the moieties -SR₅ being -SNR₇R₁₇ and -SOR₅ being -SOH;
- 20 R₇ and R₁₇ is each independently selected from hydrogen or C₁₋₄ alkyl or R₇ and R₁₇ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅;
 R₈ is C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, (CR₁₀R₂₀)_nOR₁₁, (CR₁₀R₂₀)_nS(O)_mR₁₈, (CR₁₀R₂₀)_nNHS(O)₂R₁₈, (CR₁₀R₂₀)_nNR₁₃R₁₄; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;
- 25 R₉ is hydrogen, -C(Z)R₁₁ or optionally substituted C₁₋₁₀ alkyl, S(O)₂R₁₈, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl;
- 30 R₁₀ and R₂₀ is each independently selected from hydrogen or C₁₋₄ alkyl;
 R₁₁ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroarylC₁₋₁₀ alkyl;
 R₁₂ is hydrogen or R₁₆;
- 35 R₁₃ and R₁₄ is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together

with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉;

R₁₅ is R₁₀ or C(Z)-C₁₋₄ alkyl;

- 5 R₁₆ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₇ cycloalkyl;

R₁₈ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C₁₋₁₀alkyl, heteroaryl or heteroarylalkyl;

or a pharmaceutically acceptable salt thereof.

10 **DETAILED DESCRIPTION OF THE INVENTION**

In Formula (I), suitable R₁ moieties includes 4-pyridyl, 4-pyrimidinyl, 4-pyridazinyl, 1,2,4-triazin-5-yl, 4-quinolyl, 6-isoquinolyl, 4-quinazolinyl, 1-imidazolyl and 1-benzimidazolyl rings, of which the 4-pyridyl, 4-pyrimidinyl and 4-quinolyl rings are preferred. More preferred is the 4-pyrimidinyl or 4-pyridyl

- 15 moiety, and most preferred is the 4-pyrimidinyl ring.

Suitably, the R₁ ring is optionally substituted independently one to three times with Y, NHR_a, optionally substituted C₁₋₄ alkyl, halogen, hydroxyl, optionally substituted C₁₋₄ alkoxy, optionally substituted C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amino, mono and di- C₁₋₆ alkyl substituted amino, N(R₁₀)C(O)R_b, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur.

- 20 Suitably, Y is X₁-R_a; and X₁ is oxygen or sulfur, preferably oxygen.

Suitably, R_a is C₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclicC₁₋₆alkyl, heteroaryl, or heteroarylC₁₋₆alkyl; and wherein each of these moieties may be optionally substituted. Preferably R_a is an optionally substituted C₁₋₆alkyl, aryl, or aryl C₁₋₆alkyl group.

- 30 When R_a is an aryl, it is preferably phenyl or naphthyl. When R_a is arylalkyl, it is preferably benzyl or naphthylmethyl. When R_a is a heterocyclic or heterocyclic alkyl moiety, the heterocyclic portion is preferably pyrrolindinyl, piperidine, morpholino, tetrahydropyran, tetrahydrothiopyran, tetrahydrothiopyransulfinyl, tetrahydrothio-pyransulfonyl, pyrrolindinyl, indole, or piperonyl ring. It is noted that the heterocyclic rings herein may contain unsaturation, such as in a tryptamine ring.

When R_a is a heteroaryl ring as defined below, it is preferably a pyridine or tetrazole ring.

The R_a moieties may be optionally substituted one or more times, preferably one to three times, independently with halogen; C_{1-4} alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halosubstituted alkyl, such as CF_3 ; hydroxy; hydroxy substituted C_{1-4} alkyl; $(CR_{10}R_{20})_q C_{1-4}$ alkoxy, such as methoxy or ethoxy; $(CR_{10}R_{20})_q S(O)_m$ alkyl and; $(CR_{10}R_{20})_q S(O)_m$ aryl (wherein m is 0, 1, or 2); $(CR_{10}R_{20})_q C(O)OR_{11}$, such as $C(O)C_{1-4}$ alkyl or $C(O)OH$ moieties; $(CR_{10}R_{20})_q C(O)R_{11}$; $(CR_{10}R_{20})_q OC(O)R_c$; $-O-(CH_2)_s-O-$, such as in a ketal or dioxoalkylene bridge; $(CR_{10}R_{20})_q NR_{13}R_{14}$; $(CR_{10}R_{20})_q N(R_{10})C(O)R_b$; $(CR_{10}R_{20})_q C(O)NR_{13}R_{14}$; $(CR_{10}R_{20})_q C(O)NR_{10}R_c$; $(CR_{10}R_{20})_q S(O)_2 NR_{13}R_{14}$; $(CR_{10}R_{20})_q S(O)_2 NR_{10}R_c$; $(CR_{10}R_{20})_q N(R_{10})S(O)_2 R_c$; cyano, nitro, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15} ; aryl, such as phenyl; an optionally substituted arylalkyl, such as benzyl or phenethyl; aryloxy, such as phenoxy; or arylalkyloxy such as benzyloxy; and wherein the aryl, alkylalkyl, aryloxy and arylalkyloxy moieties may be optionally substituted themselves one to two times by halogen; hydroxy; hydroxy substituted alkyl; C_{1-10} alkoxy; $S(O)_m$ alkyl; amino, NR_7R_{17} group; C_{1-4} alkyl, or halosubstituted C_{1-4} alkyl.

q is 0 or an integer having a value of 1 to 4.

R_b is suitably hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroaryl C_{1-4} alkyl, heterocyclyl, or heterocyclyl C_{1-4} alkyl moiety; all of which may be optionally substituted as defined below.

R_c is suitably an C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroaryl C_{1-4} alkyl, heterocyclyl, or heterocyclyl C_{1-4} alkyl moiety, all of which may be optionally substituted as defined below.

Suitable R_a groups include, but are not limited to, methyl, ethyl, isopropyl, benzyl, halosubstituted benzyl, naphthylmethyl, phenyl, halosubstituted phenyl, aminocarbonylphenyl, alkylphenyl, cyanophenyl, alkylthiophenyl, hydroxyphenyl, alkoxyphenyl, phenoxyphenyl, benzyloxyphenyl, phenylphenyl, methylenedioxyphenyl, trifluoromethylphenyl, methylsulfonylphenyl, tetrazole, methyltetrazolyl, morpholinopropyl, piperonyl, piperidin-4-yl, alkyl substituted piperidine, such as 1-methyl piperidine, or 2,2,6,6-tetramethylpiperidin-4-yl.

When the R₁ optional substituent is N(R₁₀)C(O) R_B, R_B is preferably a C₁₋₆ alkyl and R₁₀ is preferably hydrogen. It is also recognized that the R_B moieties, in particular the C₁₋₆ alkyl group may be optionally substituted, preferably from one to three times, preferably with halogen, such as fluorine, as in trifluoromethyl or trifluoroethyl.

Preferably R₁ is substituted by Y, such as alkoxy, aryloxy, or arylalkyloxy, NHRa, or amino. A preferred ring placement of the R₁ substituent on the 4-pyridyl derivative is the 2-position, such as 2-methoxy-4-pyridyl. A preferred ring placement on the 4-pyrimidinyl ring is also at the 2-position, such as in 2-methoxy-pyrimidinyl.

Preferably, when the substituent is an optionally substituted C₁₋₄ alkyl. The alkyl moiety is preferably substituted by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy, such as hydroxyethoxy; C₁₋₁₀ alkoxy, such as a methoxymethoxy, S(O)_m alkyl, wherein m is 0, 1 or 2; amino, mono & di-substituted amino, such as in the NR₇R₁₇ group, i.e. tert-butylaminoethoxy; or where the R₇R₁₇ may together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C₁₋₁₀ alkyl, cycloalkyl, or cycloalkyl alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; or halosubstituted C₁₋₁₀ alkyl, such as CF₃. Preferably the R₁ substituents are tertbutylaminoethoxy, or hydroxyethoxy.

Suitably, R₄ is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents. More preferably R₄ is a phenyl or naphthyl ring. Suitable substitutions for R₄ when this is a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl moiety are one or two substituents each of which are independently selected from halogen, SR₅, SOR₅, OR₁₂, CF₃, or (CR₁₀R₂₀)_vNR₁₀R₂₀, and for other positions of substitution on these rings preferred substitution is halogen, S(O)_mR₃, OR₃, CF₃, (CR₁₀R₂₀)_mNR₁₃R₁₄, NR₁₀C(Z)R₃ and NR₁₀S(O)_mR₈. Preferred substituents for the 4-position in phenyl and naphth-1-yl and on the 5-position in naphth-2-yl include halogen, especially fluoro and chloro and -SR₅ and -SOR₅ wherein R₅ is preferably a C₁₋₂ alkyl, more preferably methyl; of which the fluoro and chloro is more preferred, and most especially preferred is fluoro. Preferred substituents for the 3-position in

phenyl and naphth-1-yl rings include: halogen, especially fluoro and chloro; OR₃, especially C₁₋₄ alkoxy; CF₃; NR₁₀R₂₀, such as amino; -NR₁₀C(Z)R₃, especially NHCO(C₁₋₁₀ alkyl); NR₁₀S(O)_mR₈, especially NHSO₂(C₁₋₁₀ alkyl), and SR₃ and -SOR₃ wherein R₃ is preferably a C₁₋₂ alkyl, more preferably methyl. When the phenyl ring is disubstituted preferably it is two independent halogen moieties, such as fluoro and chloro, preferably di-chloro and more preferably in the 3, 4-position. It is also preferred that for the 3-position of both the OR₃ and ZC(Z)R₃ moieties, R₃ may also include hydrogen.

Preferably, the R₄ moiety is an unsubstituted or substituted phenyl moiety. More preferably, R₄ is phenyl or phenyl substituted at the 4-position with fluoro and/or substituted at the 3-position with fluoro, chloro, C₁₋₄ alkoxy, methane-sulfonamido or acetamido, or R₄ is a phenyl di-substituted at the 3,4-position independently with chloro or fluoro, more preferably chloro. Most preferably, R₄ is a 4-fluorophenyl.

Suitably, R₄ is an optionally substituted phenyl. Preferably the phenyl is substituted one or more times independently by halogen, -SR₅, -S(O)R₅, -OR₁₂, halo-substituted-C₁₋₄ alkyl, or C₁₋₄ alkyl.

As used herein, "optionally substituted" unless specifically defined herein, shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C₁₋₁₀alkyl; C₁₋₁₀ alkoxy, such as methoxy or ethoxy; S(O)_m alkyl, wherein m is 0, 1 or 2, such as methyl thio, methylsulfanyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR₇R₁₇ group; or where the R₇R₁₇ may together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, or C₃₋₇ cycloalkyl alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; halosubstituted C₁₋₁₀ alkyl, such CF₃; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, wherein these aryl moieties may also be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C₁₋₁₀ alkoxy; S(O)_m alkyl; amino, mono & di-substituted amino, such as in the NR₇R₁₇ group; alkyl, or CF₃.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane

sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula (1) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

- 10 The following terms, as used herein, refer to:
- "halo" or "halogens", include the halogens: chloro, fluoro, bromo and iodo.
 - "C₁₋₁₀alkyl" or "alkyl" - both straight and branched chain radicals of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
 - "aryl" - phenyl and naphthyl.
 - "cycloalkyl" is used herein to mean cyclic radicals, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
 - "heteroaryl" (on its own or in any combination, such as "heteroarylloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited to, pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quiazolinyl, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.
 - "heterocyclic" (on its own or in any combination, such as "heterocyclylalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydro pyran, or imidazolidine.
 - The term "aralkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean C₁₋₄ alkyl as defined above attached to an aryl, heteroaryl or heterocyclic moiety as also defined herein unless otherwise indicate.

• "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized S (O)₂ moiety.

For the purposes herein the "core" 4-pyrimidinyl moiety for R₁ is referred to as the formula:



Exemplified compounds of Formula (I) include:

- 4-(4-Fluorophenyl)-5-(4-pyridyl)imidazole
- 10 4-(4-Fluorophenyl)-5-(2-methoxy-pyrimidin-4-yl)imidazole
- 4-(4-Fluorophenyl)-5-(2-methylthio-pyrimidin-4-yl)imidazole

The compounds of Formula (I) may be obtained by applying synthetic procedures as described in USSN 08/091,491, published as Adams et al. WO95/02575; US patent 5,593,992 Adams et al.; and USSN 08/659,102 published as PCT US96/40143. Synthetic chemistry for each of the variously substituted R₁ moieties is contained within each noted patent application. A description of the assay for inhibition of the cytokine specific binding protein (CSBP) is also found in WO95/07922 (Attorney Docket No.: P50195-1). Each of these references is incorporated herein in their entirety.

Pharmaceutically acid addition salts of compounds of Formula (I) may be obtained in known manner, for example by treatment thereof with an appropriate amount of acid in the presence of a suitable solvent.

METHODS OF TREATMENT

The compounds of Formula (I), or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated cytokine production by such mammal's cell, such as but not limited to monocytes and/or macrophages.

Compounds of Formula (I) are capable of inhibiting proinflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF and are therefore of use in therapy. IL-1, IL-6, IL-8 and TNF affect a wide variety of cells and tissues and these cytokines, as well as other leukocyte-derived cytokines, are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these pro-inflammatory cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

Accordingly, the present invention provides a method of treating a cytokine-mediated disease which comprises administering an effective cytokine-interfering amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

Compounds of Formula (I) are capable of inhibiting inducible proinflammatory proteins, such as COX-2, also referred to by many other names such as prostaglandin endoperoxide synthase-2 (PGHS-2) and are therefore of use in therapy. These proinflammatory lipid mediators of the cyclooxygenase (CO) pathway are produced by the inducible COX-2 enzyme. Regulation, therefore of COX-2 which is responsible for the these products derived from arachidonic acid, such as prostaglandins affect a wide variety of cells and tissues are important and critical inflammatory mediators of a wide variety of disease states and conditions. Expression of COX-1 is not effected by compounds of Formula (I). This selective inhibition of COX-2 may alleviate or spare ulcerogenic liability associated with inhibition of COX-1 thereby inhibiting prostoglandins essential for cytoprotective effects. Thus inhibition of these pro-inflammatory mediators is of benefit in controlling, reducing and alleviating many of these disease states. Most notably these inflammatory mediators, in particular prostaglandins, have been implicated in pain, such as in the sensitization of pain receptors, or edema. This aspect of pain management therefore includes treatment of neuromuscular pain, headache, cancer pain, and arthritis pain. Compounds of Formula (I) or a pharmaceutically acceptable salt thereof, are of use in the prophylaxis or therapy in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

Accordingly, the present invention provides a method of inhibiting the synthesis of COX-2 which comprises administering an effective amount of a

compound of Formula (I) or a pharmaceutically acceptable salt thereof. The present invention also provides for a method of prophylaxis treatment in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

5 A new member of the MAP kinase family, alternatively termed CSBP, p38, or RK, has been identified independently by several laboratories recently. Activation of this novel protein kinase via dual phosphorylation has been observed in different cell systems upon stimulation by a wide spectrum of stimuli, such as physicochemical stress and treatment with lipopolysaccharide
10 or proinflammatory cytokines such as interleukin-1 and tumor necrosis factor. The cytokine biosynthesis inhibitors, of the present invention, compounds of Formula (I), have been determined to be potent and selective inhibitors of CSBP/p38/RK kinase activity. These inhibitors are of aid in determining the signaling pathways involvement in inflammatory responses. In particular, for
15 the first time a definitive signal transduction pathway can be prescribed to the action of lipopolysaccharide in cytokine production in macrophages.

 The cytokine inhibitors were subsequently tested in a number of animal models for anti-inflammatory activity. Model systems were chosen that were
20 relatively insensitive to cyclooxygenase inhibitors in order to reveal the unique activities of cytokine suppressive agents. The inhibitors exhibited significant activity in many such in vivo studies. Most notable are its effectiveness in the collagen-induced arthritis model and inhibition of TNF production in the endotoxic shock model. In the latter study, the reduction in plasma level of
25 TNF correlated with survival and protection from endotoxic shock related mortality. Also of great importance are the compounds effectiveness in inhibiting bone resorption in a rat fetal long bone organ culture system.
 Griswold et al., (1988) *Arthritis Rheum.* 31:1406-1412; Badger, et al., (1989) *Circ. Shock* 27, 51-61; Votta et al., (1994) *in vitro. Bone* 15, 533-538; Lee et al.,
30 (1993). *B Ann. N. Y. Acad. Sci.* 696, 149-170.

 Another aspect of the present invention, therefore, is the treatment of a CSBP/RK/p38 kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of
35 Formula (I). Suitable diseases, include those mentioned herein for IL-1, IL-6, IL-8 and TNF and more specifically those disease which are CSBP/RK/p38

kinase mediated diseases. These include, but are not limited to rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke,

5 reperfusion injury, CNS injuries, such as neurotrauma and ischemia, including both open and closed head injuries), psoriasis, restenosis, such as occurs following coronary angioplasty, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, osteoporosis, , graft vs. host reaction, allograft rejections, Crohn's disease,

10 ulcerative colitis or any other anti-inflammatory bowel disease (IBD), or pyresis.

CNS injuries as defined herein include both open or penetrating head trauma, such as by surgery, or a closed head trauma injury, such as by an injury

15 to the head region. Also included within this definition is ischemic stroke, particularly to the brain area.

Ischemic stroke may be defined as a focal neurologic disorder that results from insufficient blood supply to a particular brain area, usually as a

20 consequence of an embolus, thrombi, or local atheromatous closure of the blood vessel. The role of inflammatory cytokines in this are has been emerging and the present invention provides a mean for the potential treatment of these injuries. Relatively little treatment, for an acute injury such as these has been available.

25

TNF- α is a cytokine with proinflammatory actions, including endothelial leukocyte adhesion molecule expression. Leukocytes infiltrate into ischemic brain lesions and hence compounds which inhibit or decrease levels of TNF would be useful for treatment of ischemic brain injury. See Liu et al.,

30 Stoke, Vol. 25., No. 7, pp 1481-88 (1994) whose disclosure is incorporated herein by reference.

Models of closed head injuries and treatment with mixed 5-LO/CO agents is discussed in Shohami et al., J. of Vaise & Clinical Physiology and

35 Pharmacology, Vol. 3, No. 2, pp. 99-107 (1992) whose disclosure is

incorporated herein by reference. Treatment which reduced edema formation was found to improve functional outcome in those animals treated.

Another aspect of the present invention is to use of a compound of Formula (I) for the treatment of chronic inflammatory or proliferative or angiogenic diseases which are caused by excessive, inappropriate angiogenesis. Compounds of Formula (I) may also be used topically in the treatment or prophylaxis of disease states exacerbated by excessive or inappropriate angiogenesis.

Chronic diseases which have an inappropriate angiogenic component are various ocular neovascularizations, such as diabetic retinopathy and macular degeneration.

Other chronic diseases which have an excessive or increased proliferation of vasculature are tumor growth and metastasis, atherosclerosis, and certain arthritic conditions. Therefore cytokine inhibitors will be of utility in the blocking of the angiogenic component of these disease states.

The term "excessive or increased proliferation of vasculature inappropriate angiogenesis" as used herein includes, but is not limited to, diseases which are characterized by hemangiomas and ocular diseases.

The term "inappropriate angiogenesis" as used herein includes, but is not limited to, diseases which are characterized by vesicle proliferation with accompanying tissue proliferation, such as occurs in cancer, metastasis, arthritis and atherosclerosis.

The murine airpouch granuloma model of chronic inflammation (Kimura et al., 1985, J. Pharmacobio-Dyn., 8:393-400; Colville-Nash et al., 1995, J. Pharm. and Exp. Ther., 274:1463-1472) whose disclosure is incorporated herein by reference in its entirety, is characterized by inflammatory cell influx, fibrous tissue proliferation and intense angiogenesis. It is representative of inflammatory angiogenesis and demonstrates that the angiogenic component can be pharmacologically modulated independently of granuloma growth and size. In addition, angiogenesis can be accurately quantitated by a vascular casting method. For additional information on screening, etc., see Winkler et al., USSN 60/013,138 now PCT/US97/03626, filed 03/07/97, Attorney Docket No.: P50450-1, whose disclosure is incorporated herein by reference.

In particular, compounds of Formula (I) or a pharmaceutically acceptable salt thereof are of use in the prophylaxis or therapy of any disease

state in a human, or other mammal, which is exacerbated by or caused by excessive or unregulated IL-1, IL-8 or TNF production by such mammal's cell, such as, but not limited to, monocytes and/or macrophages.

- 5 Accordingly, in another aspect, this invention relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

 There are many disease states in which excessive or unregulated IL-1
10 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, stroke, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, muscle degeneration, multiple sclerosis, cachexia,
15 bone resorption, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes, pancreatic β cells and Alzheimer's disease.

 In a further aspect, this invention relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering
20 to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

 Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic
25 conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as
30 influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

 Compounds of Formula (I) are also useful in the treatment of viral
35 infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. The viruses contemplated for treatment herein are

those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibiting-compounds of Formula (1). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as but not limited to, Herpes Zoster and Herpes Simplex. Accordingly, in a further aspect, this invention relates to a method of treating a mammal afflicted with a human immunodeficiency virus (HIV) which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

Compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than in humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to, lentivirus infections such as, equine infectious anaemia virus, caprine arthritis virus, visna virus, or maedi virus or retrovirus infections, such as but not limited to feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus or other retroviral infections.

The compounds of Formula (I) may also be used topically in the treatment or prophylaxis of topical disease states mediated by or exacerbated by excessive cytokine production, such as by IL-1 or TNF respectively, such as inflamed joints, eczema, psoriasis and other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

Compounds of Formula (I) have also been shown to inhibit the production of IL-8 (Interleukin-8, NAP). Accordingly, in a further aspect, this invention relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. These diseases are characterized by massive neutrophil infiltration such as, psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. All of these

diseases are associated with increased IL-8 production which is responsible for the chemotaxis of neutrophils into the inflammatory site. In contrast to other inflammatory cytokines (IL-1, TNF, and IL-6), IL-8 has the unique property of promoting neutrophil chemotaxis and activation. Therefore, the inhibition of

5 IL-8 production would lead to a direct reduction in the neutrophil infiltration.

The compounds of Formula (I) are administered in an amount sufficient to inhibit cytokine, in particular IL-1, IL-6, IL-8 or TNF, production such that it is regulated down to normal levels, or in some case to subnormal levels, so as to ameliorate or prevent the disease state. Abnormal levels of IL-1, IL-6, IL-8 or
10 TNF, for instance in the context of the present invention, constitute: (i) levels of free (not cell bound) IL-1, IL-6, IL-8 or TNF greater than or equal to 1 picogram per ml; (ii) any cell associated IL-1, IL-6, IL-8 or TNF; or (iii) the presence of IL-1, IL-6, IL-8 or TNF mRNA above basal levels in cells or tissues in which IL-1, IL-6, IL-8 or TNF, respectively, is produced.

15 The discovery that the compounds of Formula (I) are inhibitors of cytokines, specifically IL-1, IL-6, IL-8 and TNF is based upon the effects of the compounds of Formulas (I) on the production of the IL-1, IL-8 and TNF in *in vitro* assays which are described herein.

As used herein, the term "inhibiting the production of IL-1 (IL-6, IL-8 or
20 TNF)" refers to:

- a) a decrease of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels by inhibition of the *in vivo* release of the cytokine by all cells, including but not limited to monocytes or macrophages;
- 25 b) a down regulation, at the genomic level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels;
- c) a down regulation, by inhibition of the direct synthesis of the cytokine (IL-1, IL-6, IL-8 or TNF) as a posttranslational event; or
- 30 d) a down regulation, at the translational level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels.

As used herein, the term "TNF mediated disease or disease state" refers
35 to any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another monokine to be released, such as but not

limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF.

5 As used herein, the term "cytokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce them. For instance, a monokine
10 is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells however also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes and B-lymphocytes. Lymphokines are generally referred
15 to as being produced by lymphocyte cells. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF-a) and Tumor Necrosis Factor beta (TNF-B).

As used herein, the term "cytokine interfering" or "cytokine suppressive
20 amount" refers to an effective amount of a compound of Formula (I) which will cause a decrease in the *in vivo* levels of the cytokine to normal or sub-normal levels, when given to a patient for the prophylaxis or treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production.

25 As used herein, the cytokine referred to in the phrase "inhibition of a cytokine, for use in the treatment of a HIV-infected human" is a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle
30 degeneration.

As TNF-B (also known as lymphotoxin) has close structural homology with TNF-a (also known as cachectin) and since each induces similar biologic responses and binds to the same cellular receptor, both TNF-a and TNF-B are inhibited by the compounds of the present invention and thus are herein referred
35 to collectively as "TNF" unless specifically delineated otherwise.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be Formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition
5 comprising an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent.

Compounds of Formula (I), pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration,
10 for instance, orally, topically, parenterally or by inhalation. The compounds of Formula (I) may be administered in conventional dosage forms prepared by combining a compound of Formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of Formula (I) may also be administered in conventional dosages in combination with a known, second
15 therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration
20 and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the Formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc,
25 gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

30 A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg. to about 1g. When a liquid carrier is used, the preparation will be in the
35 form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

Compounds of Formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of Formula (I) externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the Formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the Formulation.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100° C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Compounds of formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parental administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. Compounds of Formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

For all methods of use disclosed herein for the compounds of Formula (I), the daily oral dosage regimen will preferably be from about 0.01 to about 80 mg/kg of total body weight, preferably from about 0.1 to 30 mg/kg, more preferably from about 0.2 mg to 15 mg. The daily parenteral dosage regimen about 0.01 to about 80 mg/kg of total body weight, preferably from about 0.1 to about 30 mg/kg, and more preferably from about 0.2 mg to 15mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be

determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The novel compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than humans, in need of inhibition of cytokine inhibition or production. In particular, cytokine mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted herein in the Methods of Treatment section, but in particular viral infections. Examples of such viruses include, but are not limited to, lentivirus infections such as, equine infectious anaemia virus, caprine arthritis virus, visna virus, or maedi virus or retrovirus infections, such as but not limited to feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus or other retroviral infections.

The invention will now be described by reference to the following biological examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

BIOLOGICAL EXAMPLES

The cytokine-inhibiting effects of compounds of the present invention were determined by the following *in vitro* assays:

Interleukin - 1 (IL-1)

Human peripheral blood monocytes are isolated and purified from either fresh blood preparations from volunteer donors, or from blood bank buffy coats, according to the procedure of Colotta *et al.*, J Immunol, 132, 936 (1984). These monocytes (1×10^6) are plated in 24-well plates at a concentration of 1-2 million/ml per well. The cells are allowed to adhere for 2 hours, after which time non-adherent cells are removed by gentle washing. Test compounds are then added to the cells for 1h before the addition of lipopolysaccharide (50 ng/ml), and the cultures are incubated at 37°C for an additional 24h. At the end of this period, culture supernatants are removed and clarified of cells and all debris. Culture supernatants are then immediately assayed for IL-1 biological activity, either by the method of Simon *et al.*, J. Immunol. Methods, 84, 85, (1985) (based on ability of IL-1 to stimulate a Interleukin 2 producing cell line

(EL-4) to secrete IL-2, in concert with A23187 ionophore) or the method of Lee *et al.*, *J. ImmunoTherapy*, 6 (1), 1-12 (1990) (ELISA assay).

Tumour Necrosis Factor (TNF):

5 Human peripheral blood monocytes are isolated and purified from either blood bank buffy coats or platelet pheresis residues, according to the procedure of Colotta, R. *et al.*, *J Immunol*, **132**(2), 936 (1984). The monocytes are plated at a density of 1×10^6 cells/ml medium/well in 24-well multi-dishes. The cells are allowed to adhere for 1 hour after which time the supernatant is aspirated
10 and fresh medium (1ml, RPMI-1640, Whitaker Biomedical Products, Whitaker, CA) containing 1% fetal calf serum plus penicillin and streptomycin (10 units/ml) added. The cells are incubated for 45 minutes in the presence or absence of a test compound at 1nM-10mM dose ranges (compounds are solubilized in dimethyl sulfoxide/ethanol, such that the final solvent
15 concentration in the culture medium is 0.5% dimethyl sulfoxide/0.5% ethanol). Bacterial lipopolysaccharide (*E. coli* 055:B5 [LPS] from Sigma Chemicals Co.) is then added (100 ng/ml in 10 ml phosphate buffered saline) and cultures incubated for 16-18 hours at 37°C in a 5% CO₂ incubator. At the end of the incubation period, culture supernatants are removed from the cells, centrifuged
20 at 3000 rpm to remove cell debris. The supernatant is then assayed for TNF activity using either a radio-immuno or an ELISA assay, as described in WO 92/10190 and by Becker *et al.*, *J Immunol*, 1991, **147**, 4307.

IL-1 and TNF inhibitory activity does not seem to correlate with the
25 property of the compounds of Formula (I) in mediating arachidonic acid metabolism inhibition. Further the ability to inhibit production of prostaglandin and/or leukotriene synthesis, by nonsteroidal anti-inflammatory drugs with potent cyclooxygenase and/or lipoxygenase inhibitory activity does not mean that the compound will necessarily also inhibit TNF or IL-1 production, at non-
30 toxic doses.

In vivo TNF assay:

While the above indicated assay in an in vitro assay, the compounds of Formula (I) may also be tested in an in vivo system such as described in :

35 (1) "Differentiation *In Vivo* of Classical Non-Steroidal Antiinflammatory Drugs from Cytokine Suppressive Antiinflammatory Drugs and Other

Pharmacological Classes Using Mouse Tumour Necrosis Factor Alpha Production", - Griswold *et al.*, Drugs Under Exp. and Clinical Res., XIX (6), 243-248 (1993); or in

- (2) Boehm, *et al.*, 1-substituted 4-aryl-5-pyridinylimidazoles - a new class of cytokine suppressive drugs with low 5-lipoxygenase and cyclooxygenase inhibitory potency. *Journal Of Medicinal Chemistry* 39, 3929-3937 (1996) whose disclosures are incorporated by reference herein in their entirety.

Interleukin -8 (IL-8):

- Primary human umbilical cord endothelial cells (HUVEC) (Cell Systems, Kirland, Wa) are maintained in culture medium supplemented with 15% fetal bovine serum and 1% CS-HBGF consisting of aFGF and heparin. The cells are then diluted 20-fold before being plated (250 μ l) into gelatin coated 96-well plates. Prior to use, culture medium are replaced with fresh medium (200 μ l). Buffer or test compound (25 μ l, at concentrations between 1 and 10 μ M) is then added to each well in quadruplicate wells and the plates incubated for 6h in a humidified incubator at 37°C in an atmosphere of 5% CO₂. At the end of the incubation period, supernatant is removed and assayed for IL-8 concentration using an IL-8 ELISA kit obtained from R&D Systems (Minneapolis, MN). All data is presented as mean value (ng/ml) of multiple samples based on the standard curve. IC₅₀'s where appropriate are generated by non-linear regression analysis.

Cytokine Specific Binding Protein Assay

- A radiocompetitive binding assay was developed to provide a highly reproducible primary screen for structure-activity studies. This assay provides many advantages over the conventional bioassays which utilize freshly isolated human monocytes as a source of cytokines and ELISA assays to quantify them. Besides being a much more facile assay, the binding assay has been extensively validated to highly correlate with the results of the bioassay. A specific and reproducible cytokine inhibitor binding assay was developed using soluble cytosolic fraction from THP.1 cells and a radiolabeled compound. Patent Application USSN 08/123175 Lee *et al.*, filed September 1993, USSN; Lee *et al.*, PCT 94/10529 filed 16 September 1994 and Lee *et al.*, *Nature* 300, n(72), 739-746 (Dec. 1994) whose disclosures are incorporated by reference herein in its entirety describes the above noted method for screening drugs to identify compounds which interact with and bind to the cytokine specific binding

- protein (hereinafter CSBP). However, for purposes herein the binding protein may be in isolated form in solution, or in immobilized form, or may be genetically engineered to be expressed on the surface of recombinant host cells such as in phage display system or as fusion proteins. Alternatively, whole cells
- 5 or cytosolic fractions comprising the CSBP may be employed in the screening protocol. Regardless of the form of the binding protein, a plurality of compounds are contacted with the binding protein under conditions sufficient to form a compound/ binding protein complex and compound capable of forming, enhancing or interfering with said complexes are detected.
- 10 Representative compounds of Formula (I), Examples 1 to 3 have all demonstrated positive inhibitory activity in this binding assay.

CSBP Kinase Assay:

- This assay measures the CSBP-catalyzed transfer of ^{32}P from [α - ^{32}P]ATP to
- 15 threonine residue in an epidermal growth factor receptor (EGFR)-derived peptide (T669) with the following sequence: KRELVEPLTPSGEAPNQALLR (residues 661-681). (See Gallagher et al., "Regulation of Stress Induced Cytokine Production by Pyridinyl Imidazoles: Inhibition of CSPB Kinase", BioOrganic & Medicinal Chemistry, to be published 1996).
- 20 Kinase reactions (total volume 30 μl) contain: 25 mM Hepes buffer, pH 7.5; 10 mM MgCl_2 ; 170 μM ATP⁽¹⁾; 10 μM Na ortho vanadate; 0.4 mM T669 peptide; and 20-80 ng of yeast-expressed purified CSBP2 (see Lee et al., *Nature* 300, n(72), 739-746 (Dec. 1994)). Compounds (5 μl from [6X] stock⁽²⁾) are pre-incubated with the enzyme and peptide for 20 min on ice prior to starting the reactions with
- 25 ^{32}P /MgATP. Reactions are incubated at 30 $^\circ\text{C}$ for 10 min and stopped by adding 10 μl of 0.3 M phosphoric acid. ^{32}P -labeled peptide is separated on phosphocellulose (Wattman, p81) filters by spotting 30 μl reaction mixture. Filters are washed 3 times with 75 mM phosphoric acid followed by 2 washes with H_2O , and counted for ^{32}P .
- (1) The K_m of CSBP for ATP was determined to be 170 μM . Therefore,
- 30 compounds screened at the K_m value of ATP.
- (2) Compounds are usually dissolved in DMSO and are diluted in 25 mM Hepes buffer to get final concentration of DMSO of 0.17%.

Prostaglandin endoperoxide synthase-2 (PGHS-2) assay:

- 35 The following assay describes a method for determining the inhibitory effects of compounds of Formula (I) on human PGHS-2 protein expression in

LPS stimulated human monocytes. The assay shown below is demonstrated with compounds other than that of Formula (I) herein:

Method: Human peripheral blood monocytes were isolated from buffy coats by centrifugation through Ficoll and Percoll gradients. Cells were seeded at 2 X 10⁶/well in 24 well plates and allowed to adhere for 1 hour in RPMI supplemented with 1% human AB serum, 20mM L-glutamine, Penicillin-Streptomycin and 10mM HEPES. Compounds were added at various concentrations and incubated at 37°C for 10 minutes. LPS was added at 50 ng/well (to induce enzyme expression) and incubated overnight at 37°C. The supernatant was removed and cells washed once in cold PBS. The cells were lysed in 100µl of cold lysis buffer(50mM Tris/HCl pH 7.5, 150mM NaCl, 1% NP40, 0.5% sodium deoxycholate, 0.1% SDS, 300µg/ml DNAse, 0.1% TRITON X-100, 1mM PMSF, 1mM leupeptin, 1mM pepstatin). The lysate was centrifuged (10,000 X g for 10 min. at 4°C) to remove debris and the soluble fraction was subjected to SDS PAGE. analysis (12% gel). Protein separated on the gel were transferred onto nitrocellulose membrane by electrophoretic means for 2 hours at 60 volts. The membrane was pretreated for one hour in PBS/0.1% Tween 20 with 5% non-fat dry milk. After washing 3 times in PBS/Tween buffer, the membrane was incubated with a 1:2000 dilution of a monospecific antiserum to PGHS-2 or a 1:1000 dilution of an antiserum to PGHS-1 in PBS/Tween with 1% BSA for one hour with continuous shaking. The membrane was washed 3X in PBS/Tween and then incubated with a 1:3000 dilution of horseradish peroxidase conjugated donkey antiserum to rabbit Ig (Amersham) in PBS/Tween with 1% BSA for one hour with continuous shaking. The membrane was then washed 3X in PBS/Tween and the ECL immunodetection system (Amersham) was used to detect the level of expression of prostaglandin endoperoxide synthases-2.

Results: The following compounds were tested and found to be active in this assay (i.e., inhibited LPS induced PGHS-2 protein expression in rank order potency similar to that for inhibiting cytokine production as noted in assays indicated): 6-(4-Fluoro-phenyl)-2,3-dihydro-5-(4-pyridinyl)imidazo[2,1-b]thiazole; and Dexamethasone

Several compounds were tested and found to be inactive (up to 10µM): 2-(4-Methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-(5H)-pyrrolo[1,2-a]imidazole; rolipram ; phenidone and NDGA. None of these compounds

tested were found to inhibit PGHS-1 or cPLA₂ protein levels in similar experiments.

TNF- α in Traumatic Brain Injury Assay

- 5 The present assay provides for examination of the expression of tumor necrosis factor mRNA in specific brain regions which follow experimentally induced lateral fluid-percussion traumatic brain injury (TBI) in rats. Adult Sprague-Dawley rats (n=42) are anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and subjected to lateral fluid-percussion brain injury of moderate
- 10 severity (2.4 atm.) centered over the left temporoparietal cortex (n=18), or "sham" treatment (anesthesia and surgery without injury, n=18). Animals are sacrificed by decapitation at 1, 6 and 24 hr. post injury, brains removed, and tissue samples of left (injured) parietal cortex (LC), corresponding area in the contralateral right cortex (RC), cortex adjacent to injured parietal cortex (LA),
- 15 corresponding adjacent area in the right cortex (RA), left hippocampus (LH) and right hippocampus (RH) are prepared. Total RNA is isolated and Northern blot hybridization is performed and quantitated relative to an TNF- α positive control RNA (macrophage = 100%). A marked increase of TNF- α mRNA expression is observed in LH (104 \pm 17% of positive control, p < 0.05 compared
- 20 with sham), LC (105 \pm 21%, p < 0.05) and LA (69 \pm 8%, p < 0.01) in the traumatized hemisphere 1 hr. following injury. An increased TNF- α mRNA expression is also observed in LH (46 \pm 8%, p < 0.05), LC (30 \pm 3%, p < 0.01) and LA (32 \pm 3%, p < 0.01) at 6 hr. which resolves by 24 hr. following injury. In the contralateral hemisphere, expression of TNF- α mRNA is increased in RH
- 25 (46 \pm 2%, p < 0.01), RC (4 \pm 3%) and RA (22 \pm 8%) at 1 hr. and in RH (28 \pm 11%), RC (7 \pm 5%) and RA (26 \pm 6%, p < 0.05) at 6 hr. but not at 24 hr. following injury. In sham (surgery without injury) or naive animals, no consistent changes in expression of TNF- α mRNA is observed in any of the 6 brain areas in either hemisphere at any times. These results indicate that following
- 30 parasagittal fluid-percussion brain injury, the temporal expression of TNF- α mRNA is altered in specific brain regions, including those of the non-traumatized hemisphere. Since TNF- α is able to induce nerve growth factor (NGF) and stimulate the release of other cytokines from activated astrocytes, this post-traumatic alteration in gene expression of TNF- α plays an important
- 35 role in both the acute and regenerative response to CNS trauma.

CNS Injury model for IL- β mRNA

This assay characterizes the regional expression of interleukin-1 β (IL-1 β) mRNA in specific brain regions following experimental lateral fluid-percussion traumatic brain injury (TBI) in rats. Adult Sprague-Dawley rats (n=42) are anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and subjected to lateral fluid-percussion brain injury of moderate severity (2.4 atm.) centered over the left temporoparietal cortex (n=18), or "sham" treatment (anesthesia and surgery without injury). Animals are sacrificed at 1, 6 and 24 hr. post injury, brains removed, and tissue samples of left (injured) parietal cortex (LC), corresponding area in the contralateral right cortex (RC), cortex adjacent to injured parietal cortex (LA), corresponding adjacent area in the right cortex (RA), left hippocampus (LH) and right hippocampus (RH) were prepared. Total RNA is isolated and Northern blot hybridization is performed and the quantity of brain tissue IL-1 β mRNA is presented as percent relative radioactivity of IL-1 β positive macrophage RNA which is loaded on same gel. At 1 hr. following brain injury, a marked and significant increase in expression of IL-1 β mRNA is observed in LC ($20.0 \pm 0.7\%$ of positive control, n=6, $p < 0.05$ compared with sham animal), LH ($24.5 \pm 0.9\%$, $p < 0.05$) and LA ($21.5 \pm 3.1\%$, $p < 0.05$) in the injured hemisphere, which remained elevated up to 6 hr. post injury in the LC ($4.0 \pm 0.4\%$, n=6, $p < 0.05$) and LH ($5.0 \pm 1.3\%$, $p < 0.05$). In sham or naive animals, no expression of IL-1 β mRNA is observed in any of the respective brain areas. These results indicate that following TBI, the temporal expression of IL-1 β mRNA is regionally stimulated in specific brain regions. These regional changes in cytokines, such as IL-1 β play a role in the post-traumatic pathologic or regenerative sequelae of brain injury.

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade, all solvents are highest available purity and all reactions run under anhydrous conditions in an argon atmosphere unless otherwise indicated.

In the Examples, all temperatures are in degrees Centigrade ($^{\circ}\text{C}$). Mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment, unless otherwise indicated. ^1H -NMR (hereinafter "NMR") spectra were recorded at 250 MHz using a Bruker AM 250 or Am 400

spectrometer. Multiplicities indicated are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br indicates a broad signal. Sat. indicates a saturated solution, eq indicates the proportion of a molar equivalent of reagent relative to the principal reactant. Flash Chromatography is run over a Merck

- 5 Silica gel 60 (230-400 mesh).

Example 1

4(5)-(4-Fluorophenyl)-5(4)-(4-pyridyl)imidazole

- Pyridine-4-carboxaldehyde (321 mg, 3.0 mmol), and THF (3 mL) were cooled to
10 -50° and lithium bis(trimethylsilyl)amide (LiBSA) (1 M in THF) (3 mL, 3.0 mmol) was added dropwise (T<-40°), stirred for 45 min, and warmed to -30° for 5 min to afford Solution A.

- THF (3 mL), and 4-Fluorophenyl(tosyl)methyl isocyanide (8) (see next
experiment) (867 mg, 3.0 mmol) were cooled to -50° and LiBSA (1M in THF) (3 mL, 3.0
15 mmol) was added dropwise at -50°, stirred 30 min to afford Solution B.

- Solution A was cooled to -60° and solution B was added dropwise. The resulting
solution was stirred at -70° for 30 min, warmed to 23° over 4 h, stirred at 23° for 16 h,
poured into 5% aq Na₂CO₃ (25 mL) and extracted with EtOAc (4 x 25 mL), dried
(Na₂SO₄) concentrated and flash chromatographed (0-8% MeOH in CH₂Cl₂) to afford (28)
20 251 mg (35%). The product was crystallized from acetone/hexane: ¹H NMR 8.42 (m,2),
7.72 (s,1), 7.40 (m,4), 7.12 (m,2): MS (ES+) m/z = 240 (MH⁺): mp 245 - 246 (dec).
Anal. (C₁₄H₁₀FN₃ · 1/10 H₂O) C, H, N.

- 4-Fluorophenyl(tosyl)methyl isocyanide:** Toluenesulfonic acid sodium salt
(150g, 0.84 mol), H₂O (500 mL), and t-butylmethyl ether (TBME) (250 mL) were
25 vigorously stirred, and concd HCl (75 mL) was added dropwise. The resulting two
phases were separated and the aqueous phase was extracted with TBME (100 mL). The
TBME phases were dried (Na₂SO₄) and concentrated to near dryness and the white solid
was combined with hexane (350 mL) and filtered and dried in vacuo to afford 96g of
toluenesulfonic acid.

- The free acid (92.3 g, 0.62 mol), p-fluorobenzaldehyde (92.3 g, 0.744 mol),
formamide (73.9 mL) and camphorsulfonic acid (14.4g, 0.062 mol) were combined,
vigorously stirred and heated to 65° for 16 h. The resulting white mass was cooled to 23°,
trituted with CH₃OH (150 mL) and hexane (350 mL), filtered and dried in vacuo to
afford 88.35 g (46%) 4-fluorophenyl tosylmethylformamide as a white solid: ¹H NMR
35 8.06 (s, 1H), 7.69 (d, J = 8 Hz, 2H), 7.43 (m, 2H), 7.32 (d, J = 8 Hz, 2H), 7.08 (m, 2H),
6.29 (s, 1H), 2.43 (s, 3H).

A solution of the formamide obtained above (20.2 g, 65.7 mmol), and anhydrous DME (330 mL) was cooled to -10° and POCl₃ (18.4 mL, 197 mmol) was added dropwise. Triethylamine (45.8 mL, 329 mmol) in DME (30 mL) was added dropwise (T<-5°) and the reaction was stirred at -5° for 2h, then poured into H₂O (600 mL) and extracted with EtOAc (3 x 150 mL). The extracts were washed with satd aq NaHCO₃, dried (Na₂SO₄) and concentrated. The colorless oil was triturated with hexane to afford a solid. Filtration and drying afforded 16.2 g (85%) of 4-fluorophenyl(tosyl)methyl isocyanide as a white solid. ¹H NMR 7.62 (d, J = 8 Hz, 2H), 7.34 (m, 4H), 7.10 (m, 2H), 5.59 (s, 1H), 2.48 (s, 3H).

10

Example 2

4-(4-Fluorophenyl)-5-(2-methoxy-pyrimidin-4-yl)imidazole

Prepared by the method of example 1 except using 2-methoxypyrimidine-2-carboxaldehyde isocyanide to afford the title compound as a light brown powder. MS ES+ m/z = 271 (MH+).

15

Example 3

4-(4-Fluorophenyl)-5-(2-methylthio-pyrimidin-4-yl)imidazole

Prepared by the method of example 1 except using 2-methoxypyrimidine-2-carboxaldehyde isocyanide to afford the title compound as a light brown powder. MS ES+ m/z = 287 (MH+).

20

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

25

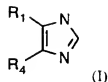
The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

30

35

WHAT IS CLAIMED IS:

1. A compound of the formula:



wherein:

- R₁ is 4-pyridyl, pyrimidinyl, 4-pyridazinyl, 1,2,4-triazin-5-yl, quinolyl, isoquinolinyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl, which heteroaryl ring is optionally substituted independently one to three times with Y, NHR_a, optionally substituted C₁₋₄ alkyl, halogen, hydroxyl, optionally substituted C₁₋₄ alkoxy, optionally substituted C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amino, mono and di- C₁₋₆ alkyl substituted amino, N(R₁₀)C(O)R_b, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur;
- Y is X₁-R_a;
- X₁ is oxygen or sulfur;
- R₄ is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, -(C(Z))NR₇R₁₇, -(C(Z))OR₁₆, -(CR₁₀R₂₀)_vCOR₁₂, -SR₅, -SOR₅, -OR₁₂, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, -ZC(Z)R₁₂, -NR₁₀C(Z)R₁₆, or -(CR₁₀R₂₀)_vNR₁₀R₂₀ and which, for other positions of substitution, is halogen, cyano, -(C(Z))NR₁₃R₁₄, -(C(Z))OR₃, -(CR₁₀R₂₀)_m-COR₃, -(S(O))_mR₃, -OR₃, halo-substituted-C₁₋₄ alkyl, -C₁₋₄ alkyl, -(CR₁₀R₂₀)_m-NR₁₀C(Z)R₃, -NR₁₀S(O)_mR₈, -NR₁₀S(O)_m-NR₇R₁₇, -ZC(Z)R₃ or -(CR₁₀R₂₀)_m-NR₁₃R₁₄;
- v is 0, or an integer having a value of 1 or 2;
- m is 0, or the integer 1 or 2;
- m' is an integer having a value of 1 or 2,
- m" is 0, or an integer having a value of 1 to 5;
- n is an integer having a value of 1 to 10;
- n' is 0, or an integer having a value of 1 to 10;
- Z is oxygen or sulfur;
- R_a is aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclylC₁₋₆alkyl, heteroaryl, heteroarylC₁₋₆alkyl, wherein each of these moieties may be optionally substituted;

- R_b is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclyl, or heterocyclylC₁₋₄ alkyl;
 R₃ is heterocyclyl, heterocyclylC₁₋₁₀ alkyl or R₈;
 R₅ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₇R₁₇, excluding the
 5 moieties -SR₅ being -SNR₇R₁₇ and -SOR₅ being -SOH;
 R₇ and R₁₇ is each independently selected from hydrogen or C₁₋₄ alkyl or R₇ and R₁₇ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅;
 10 R₈ is C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, (CR₁₀R₂₀)_nOR₁₁, (CR₁₀R₂₀)_nS(O)_mR₁₈, (CR₁₀R₂₀)_nNHS(O)₂R₁₈, (CR₁₀R₂₀)_nNR₁₃R₁₄; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;
 15 R₉ is hydrogen, C(Z)R₁₁ or optionally substituted C₁₋₁₀ alkyl, S(O)₂R₁₈, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl;
 R₁₀ and R₂₀ is each independently selected from hydrogen or C₁₋₄ alkyl;
 R₁₁ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroarylC₁₋₁₀ alkyl;
 20 R₁₂ is hydrogen or R₁₆;
 R₁₃ and R₁₄ is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or
 25 NR₉;
 R₁₅ is R₁₀ or C(Z)-C₁₋₄ alkyl;
 R₁₆ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₇ cycloalkyl;
 R₁₈ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C₁₋₁₀alkyl, heteroaryl or heteroarylalkyl;
 30 or a pharmaceutically acceptable salt thereof.
2. The compound according to Claim 1 wherein R₁ is an optionally substituted 4-pyridyl or 4-pyrimindyl.
- 35 3. The compound according to Claim 2 wherein the optional substituent is Y or NHR_a.

4. The compound according to Claim 3 wherein X₁ is oxygen and R_a is optionally substituted aryl, arylalkyl or alkyl.
5. The compound according to any of Claims 2 to 4 wherein R₄ is an optionally substituted phenyl.
6. The compound according to Claim 5 wherein the phenyl is substituted one or more times independently by halogen, SR₅, S(O)R₅, OR₁₂, halo-substituted-C₁₋₄ alkyl, or C₁₋₄ alkyl.
7. The compound according to Claim 1 which is:
4-(4-Fluorophenyl)-5-(4-pyridyl)imidazole
4-(4-Fluorophenyl)-5-(2-methoxy-pyrimidin-4-yl)imidazole
4-(4-Fluorophenyl)-5-(2-methylthio-pyrimidin-4-yl)imidazole ; or a pharmaceutically acceptable salt thereof.
8. A pharmaceutical composition comprising a compound according to any of Claims 1 to 7 and a pharmaceutically acceptable carrier or diluent.
9. A method of treating a CSBP/RK/p38 kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) according to any one of Claims 1 to 7.
10. The method according to Claim 9 wherein the mammal is afflicted with a CSBP/RK/p38 kinase mediated disease which is cytokine mediated and the disease is selected from psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic condition, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis,

multiple sclerosis, muscle degeneration, eczema, contact dermatitis, psoriasis, sunburn, and conjunctivitis.

11. The method according to Claim 10 wherein the disease is asthma,
5 osteoporosis, or arthritis.

12. A method of treating inflammation in a mammal in need thereof, which
comprises administering to said mammal an effective amount of a compound of
Formula (I) according to any of Claims 1 to 7.
10

13. A method of treating osteoporosis in a mammal in need thereof, which
comprises administering to said mammal an effective amount of a compound of
Formula (I) according to any of Claims 1 to 7.

14. A method of treating a chronic disease in a mammal in need thereof, which
disease is characterized by excessive, undesired or inappropriate angiogenesis, with
an effective amount of a compound according to any of Claims 1 to 7.
15

15. The method according to Claim 14 wherein the disease is diabetic
20 retinopathy and other ocular neovascularizations.

16. The method according to Claim 14 wherein the disease is tumor growth and
metastasis.

17. The method according to Claim 14 wherein the disease is atherosclerosis.
25

18. The method according to Claims 1 to 4 wherein the disease is arthritis.

INTERNATIONAL SEARCH REPORT

 International application No.
 PCT/US97/14731

A. CLASSIFICATION OF SUBJECT MATTER

 IPC(6) : A61K 31/44; C07D 401/04
 US CL : 514/341; 546/274.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/341; 546/274.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 5,593,991 A (ADAMS et al) 14 January 1997, columns 1 and 2, and column 62, line 24.	1,7,8,10, in part

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "B" earlier document published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"A" document member of the same patent family

Date of the actual completion of the international search

15 OCTOBER 1997

Date of mailing of the international search report

30 OCT 1997

 Name and mailing address of the ISA/US
 Commissioner of Patents and Trademarks
 Box PCT
 Washington, D.C. 20231
 Facsimile No. (703) 305-3230

Authorized officer

R. W. RAMSUER

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/14731

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-18, in part,
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US97/14731

BOX 1. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

The multitude of variables and their permutations and combinations (e.g. R1,Ra,Y,X1,Ra,Rb,R3,R5,R7,R8, etc.) result in claimed subject matter that is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Note also that the claimed subject matter lacks a significant structural element qualifying as the special technical feature that clearly defines a contribution over the art. The subject matter claimed contains an imidazole ring which does not define a contribution over the prior art. Therefore, the first discernible invention as found in Example 1, (the compound therein, the pharmaceutical composition therewith, and the method of treating psoriatic arthritis therewith) as covered by claims 1, 7, 8, and 10, has been searched.